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Regions of attainable particle sizes in continuous and batch crystallization processes

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AUTHOR-HIGHLIGHTS

- Continuous and batch crystallization processes are modeled using PBEs.
- Attainable regions (AR) in a diagram of process time vs. particle size are obtained.
- The influence of additional processing constraints on the ARs is investigated.
- The ARs show if fulfilling a set of specifications is possible in given process equipment.

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ABSTRACT

Process alternatives for continuous crystallization, i.e., cascades of mixed suspension, mixed product removal crystallizers (MSMPRCs) and plug flow crystallizers (PFCs), as well as batch crystallizers are discussed and modeled using population balance equations. The attainable region approach that has previously been used in the design of chemical reactor networks and separation systems is applied to the above-mentioned alternatives for crystallization processes in order to identify attainable regions in a diagram of mean product particle size vs. total process residence time. It is demonstrated that the boundaries of these attainable regions can be found numerically by solving appropriate optimization problems and that the region enclosed by these boundaries is fully accessible. Knowing the attainable region of particle sizes, it is possible to generate feasible process alternatives that allow specific particle sizes to be obtained in a given process configuration. The attainable regions presented in this paper are useful to determine whether a desired mean particle size can be achieved in a specific crystallizer type. The concept of the attainable region is illustrated on three case studies: the cooling crystallization of paracetamol grown from ethanol, the anti-solvent crystallization of L-asparagine monohydrate from water using isopropanol as the anti-solvent and the combined cooling/anti-solvent crystallization of aspirin from ethanol using water as the anti-solvent.

1. Introduction

Crystallization is widely used in the separation and purification of commodities, fine chemicals and active pharmaceutical ingredients (APIs). While the purity of the produced crystals is the primary concern in all of these applications, there are secondary properties, such as the crystal form and the particle size (and shape) distribution of the product crystals, that need to be considered as well. While these secondary properties merely affect further processing steps in the case of chemical intermediates (e.g., adipic acid), they are crucial in many other cases, among them the production of pigments (Brazeau et al., 2011; Liu et al., 2010), where the color, its intensity and brilliance depend on the particle size distribution and in the pharmaceutical industry, where the dissolution properties, the bioavailability and even the biocompatibility (Cavalcante et al., 2009) of an API are influenced by its particle size distribution.

In the pharmaceutical sector the vast majority of crystallization processes have been carried out for decades as batch processes and that processing method remains prevalent today (Chen et al., 2011). It is recognized that this type of operation suffers from product variability from batch-to-batch and potentially high manufacturing costs (Lawton et al., 2009; Randolph and Larson, 1988). The operation of batch crystallization processes is however quite complex and advanced control strategies are required in order to consistently fulfill product specifications, e.g., a desired

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particle size distribution (Nagy and Braatz, 2012). In contrast, continuous processes operate at steady state for which a plethora of well-established control strategies is available.

While continuous processing is a proven technique in many large scale industries for overcoming batch-to-batch variabilities and to ensure low-cost production, the pharmaceutical industry has been reluctant to embrace continuous manufacturing for two main reasons: first, the pharmaceutical industry is subject to a unique set of (regulatory) challenges; second, the low production volumes and the existing batch production capabilities rarely have justified building a dedicated continuous manufacturing plant for the production of a specific API. However, as global competition increases there is now an increased focus on reducing manufacturing costs while maintaining the high product quality that fulfills the regulatory demands.

The design methodology for batch crystallization processes has been investigated extensively and is now well understood for various combinations of cooling, anti-solvent and reactive crystallization (Genck, 2003; Larsen et al., 2006; Lindenberg et al., 2009) and for different optimization objectives (Nagy et al., 2008; Ward et al., 2006; Nagy and Braatz, 2012; Rawlings et al., 1993) (note that the list of references given is by no means exhaustive). However, there are yet relatively few studies targeted on the design and optimization of continuous crystallization processes that keep the specific challenges posed to the pharmaceutical industry in mind, e.g., Alvarez and Myerson (2010) presented a plug flow crystallizer (PFC) with incorporated static mixing elements that was used in the anti-solvent crystallization process of the API ketoconazole, and Eder et al. (2010) presented a continuously seeded PFC that was used in the cooling crystallization of aspirin from ethanol. In PFCs one of the main complications is the need to keep the crystals suspended; a feat that is typically achieved by running the PFC at high flow rates resulting in turbulent flow behavior within the pipe. Hence, using a PFC at the (low) production rates prevalent in the pharmaceutical industry is often impractical. However, Lawton et al. (2009) showed that issues with suspension can sometimes be cleverly circumvented using a continuous oscillatory baffled crystallizer resulting in a process that performs similar to an ideal PFC without the limitation of high flow rates. As an alternative, continuous crystallization processes can be operated in mixed suspension, mixed product removal crystallizers (MSMPRCs). Due to their simpler operation, they have been used in a pharmaceutical context in various configurations (single stage, multistage, with and without recycling operations, etc.) (Wong et al., 2012; Zhang et al., 2012; Alvarez et al., 2011; Quon et al., 2012) and in combination with additional product classification equipment or fines destruction loops (Griffin et al., 2010; Mersmann, 2001).

While these studies clearly show the applicability of continuous crystallization processes in the pharmaceutical industry and can serve as case studies, a process design methodology is still largely missing. In this paper, we make a contribution to such a methodology by reporting the influence of the number of stages, as well as the temperature, anti-solvent fraction and residence time in each crystallizer on the particle size distribution of the product. Specifically, we demonstrate that for any number of MSMPRCs and a constant production rate there exists a clearly defined attainable region in a diagram of mean particle size of the product crystals vs. total residence time in the MSMPRC cascade. Using extensive simulations, it will be shown that this attainable region can be entirely traversed by altering the temperature, solvent composition and residence time in each MSMPRC. Moreover, such attainable regions can also be determined for PFCs and semi-batch crystallizers by slightly adjusting the methodology used for MSMPRC cascades.

The remainder of this paper is structured as follows: In Section 2 the flowsheets and processing variants considered will be presented. Section 3 summarizes the population balance equation models used to describe the evolution of the crystal size distribution in the different crystallizers. In Section 4 the concept of the attainable region is introduced and adapted to crystallization processes. The methodology to construct these attainable regions is also explained. Finally, in Section 5 the attainable regions for different crystallizer setups (MSMPRC cascade, PFC and semi-batch) are presented for three different case studies: the cooling crystallization of paracetamol from ethanol, the anti-solvent crystallization of L-asparagine monohydrate from water using isopropanol as the anti-solvent and the combined cooling/anti-solvent crystallization of aspirin from ethanol using water as the anti-solvent. The results section of this paper is concluded by presenting the effect of additional operational constraints on the attainable regions.

2. Flowsheets for continuous and batch crystallization processes

In the pharmaceutical industry crystallization processes are usually carried out in a (semi-)batch device which is seeded and operated at low supersaturation, so that the formation of additional nuclei is avoided and the crystallization process is “growth controlled”. Such an operating policy ideally yields a unimodal size distribution in which the final size of the crystals can be conveniently tuned by choosing seed mass and size (Chung et al., 1999; Ward et al., 2006, 2011) The mean particle size of the product follows the expression $\overline{L}_f = (m_f/m_s)^{1/3}\overline{L}_s$ where m_f is the mass of isolated crystalline product, m_s is the seed mass and $\overline{L}_s$ is the mean size of the seed crystals.[1] Another distinct advantage of batch operating policies is the tight control over the crystal form (i.e., which polymorph, solvate, etc. is produced), which can be ensured by seeding the process with the desired crystal form. In a continuous process, using a classical seed procedure is impractical (and even unnecessary), so that an operating policy must include accurate knowledge of nucleation at the steady state conditions of the continuous process. In this work, we assume that nucleation behaves in a deterministic manner on the scale of the whole crystallizer, i.e., nuclei are formed at a constant rate by primary and/or secondary nucleation when the crystallizer is at steady state conditions. This assumption breaks down only for very low nucleation rates or low process volumes where the stochastic nature of nucleation becomes apparent (Kadam et al., 2011, 2012). In continuous processing, compounds that exhibit negligible nucleation rates at reasonable supersaturation levels present a challenge, as these low nucleation rates cannot sustain an appropriate number of crystals in the crystallizer. Hence, alternative ways of “nuclei generation” must be devised, such as the formation of nuclei at high supersaturations in impinging jet mixers (Woo et al., 2011) or the use of a wet mill (Kougoulos et al., 2011) to break down larger particles. The particles produced with the impinging jet mixers could then be added to the MSMPRC or PFC, while a wet mill could be used in a recycle loop where part of the product particles are fed back through the mill to undergo breakage before entering an MSMPRC cascade or a PFC. While these two techniques work in some cases, they also have their pitfalls, i.e., the formation of nuclei at high supersaturations in impinging jet mixers can lead to the nucleation of metastable crystal forms while wet milling can sometimes accelerate solvent mediated

[1] Note that in this equation we have assumed that the crystal shape does not change and that all crystallized mass is deposited on the seed crystals.